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(57) Abstract

Drugs that are freely or highly soluble in water are formulated as unit dosage forms by incorporating them into polymeric matrices comprised of high molecular weight hydrophilic polymers that swell upon imbibition of water. The dosage form can be a single compressed tablets, or two or three compressed tablets retained in a single gelatin capsule. The oral formulation is designed for gastric retention and controlled delivery of an incorporated drug into the gastric cavity, and thus administered, the drug is released from the matrix into the gastric fluid by solution diffusion. The swollen polymeric matrix, having achieved sufficient size, remains in the gastric cavity for several hours if administered while the patient is in the fed mode, and remains intact long enough for substantially all of the drug to be released before substantial erosion of the matrix occurs. The swelling matrix lowers the accessibility of the gastric fluid to the drug and thereby limits the drug release rate. This process, together with diffusion retardation by selection of specific polymers, polymer molecular weights, and other variables, results in a sustained and controlled delivery rate of the drug to the gastric environment.

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GASTRIC-RETENTIVE ORAL DRUG DOSAGE FORMS FOR CONTROLLED RELEASE OF HIGHLY SOLUBLE DRUGS

This invention is in the general field of pharmacology, and relates in particular to drug delivery systems that are retained in the stomach for an extended period of time while releasing a highly soluble drug in a controlled manner over an extended period of time, in order to achieve greater efficacy and more efficient use of the drug.

BACKGROUND OF THE INVENTION

The rate at which drugs that are administered in conventional tablets or capsules become available to body fluids is initially very high, followed by a rapid decline. For many drugs, this pattern results in a transient overdose, followed by a long period of underdosing. This is of limited clinical usefulness. The delivery pattern was improved in the 1970's with the introduction of a variety of controlled delivery systems. By providing relatively constant, controlled drug delivery, these systems avoided the overdose and the underdose effects. These improvements provided effective medication with reduced side effects, and achieved these results with reduced dosing frequency.

Many of these controlled delivery systems utilize hydrophilic, polymeric matrices that provide useful levels of control to the delivery of sparingly soluble drugs. For soluble drugs, however, and particularly for highly soluble drugs, such matrices do not provide adequate control over the drug release rate, instead resulting in a release that approximates first-order kinetics. The rate of release is therefore an inverse function of the square root of the elapsed time. With first-order release kinetics, most of the drug in the matrix is released within the first two hours in an aqueous medium.

One method of prolonging the release of a highly water-soluble drug is disclosed in International Patent Application Publication No. WO 96/26718 (Temple University; Kim, inventor). The method of this publication is the incorporation of the drug into a polymeric matrix to form a tablet that is administered orally. The polymer is water-swellable yet

erodible in gastric juices, and the polymer and the proportion of drug to polymer are chosen such that:

(i) the rate at which the polymer swells is equal to the rate at which the polymer erodes, so that the swelling of the polymer is continuously held in check by the erosion, and zero-order release kinetics of the drug from the matrix are maintained;

(ii) the release of drug from the matrix is sustained over the full erosion period of the polymer, the tablet therefore reaching full solubilization at the same time that the last of the drug is released; and

(iii) release of the drug from the matrix will be extended over a period of 24 hours.

A key disclosure in WO 96/26718 is that to achieve the release of drug in this manner requires the use of a low molecular weight polymer. If, by contrast, a high molecular weight polymer is used and the swelling rate substantially exceeds the erosion rate, the lack of erosion will prolong the diffusion of the drug residing close to the center of the tablet and prevent it from being released. Thus, there is no disclosure in WO 96/26718 that a drug of high water solubility can be released from a high molecular weight polymer in a period of time substantially less than 24 hours, or that any advantage can be obtained by the use of a polymer that does not erode as quickly as it swells. This failure is particularly significant since even swollen tablets will not remain in the stomach beyond the duration of the fed mode, which typically lasts for only 6 to 8 hours.

SUMMARY OF THE INVENTION

It has now been discovered that drugs that are highly soluble in water can be administered orally in a manner that will prolong their delivery time to extend substantially through the duration of the fed mode but not a substantial time beyond. This is achieved by using a formulation in which the drug is dispersed in a polymeric matrix that is water-swellable rather than merely hydrophilic, and that erodes at a rate that is substantially less than its swelling rate. It has further been found that the diffusion rate can be slowed by increasing the drug particle size, by the choice of polymer used in the matrix, or by the molecular weight of the polymer. The matrix is a relatively high molecular weight polymer that swells upon ingestion to achieve a size that is at least about twice its unswelled volume and that promotes gastric retention during the fed mode. Upon swelling, the matrix also converts over a prolonged period of time from a glassy polymer to a polymer that is rubbery in consistency. The penetrating fluid then causes release of the drug in a gradual and prolonged manner by the process of solution diffusion, *i.e.*,

dissolution of the drug in the penetrating fluid and diffusion of the dissolved drug back out of the matrix. The matrix itself is solid prior to administration and, once administered, remains undissolved in (*i.e.*, uneroded by) the gastric fluid for a period of time sufficient to permit the majority of the drug to be released by the solution diffusion process during the fed mode. The rate-limiting factor in the release of the drug is therefore controlled diffusion of the drug from the matrix rather than erosion, dissolution or chemical decomposition of the matrix.

The swelling of the polymeric matrix thus achieves two results -- (i) it swells the matrix to a size large enough to cause it to be retained in the stomach during the fed mode, and (ii) it retards the rate of diffusion of a highly soluble drug long enough to provide multi-hour, controlled delivery of the drug into the stomach. This combination of gastric retention and controlled delivery of soluble drugs provides an effective means of using these drugs to treat local stomach disorders. For example, use of this invention provides more effective eradication of an ulcer-causing bacterium in the gastric mucosa with soluble antibiotics. The invention also provides enhanced absorption of soluble drugs that are absorbed mostly in the stomach or high in the gastrointestinal tract, such as metformin hydrochloride or ciprofloxacin. The invention is also useful in providing a multi-hour flow of a drug past the upper part of the small intestine (the most efficient absorption site for many agents).

Details of these and other features of the invention will be apparent from the description that follows.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a plot showing the release rate of metformin hydrochloride from three different compositions of the drug in poly(ethylene oxide) matrices.

FIG. **2** is a plot showing the release rate of captopril from a poly(ethylene oxide) matrix, in accordance with this invention, both with and without glyceryl monostearate as a solubility modifier.

FIG. **3** is a plot showing the release rate of captopril from hydroxyethyl cellulose, in which the pellet size was varied.

FIG. **4** is a plot showing the release rate of metformin hydrochloride from various polymeric matrices.

FIG. **5** is a plot showing the release rate of metformin hydrochloride from a single capsule-shaped pellet.

FIG. **6** is a plot showing the release rate of captopril from various polymeric matrices.

FIG. 7 is a plot showing further release rate studies of metformin hydrochloride from two different polymeric matrices.

FIG. 8 is a plot showing the release rate of vancomycin hydrochloride from different polymeric matrices.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

Drugs to which the present invention applies are those that are characterized by the United States Pharmacopeia XXII as at least "freely soluble" in water, *i.e.*, one part of the drug dissolves in less than about ten parts of water. Drugs of particular interest are those that require only about five parts of water or less (per one part of drug) to dissolve, and drugs of even greater interest are those that require only about three parts of water or less. The parts referred to in this paragraph are parts by weight.

The term "drug" is used herein to denote any chemical compound, complex or composition that is suitable for oral administration and that has a beneficial biological effect, preferably a therapeutic effect in the treatment of a disease or abnormal physiological condition. Examples of drugs to which this invention is applicable are metformin hydrochloride, captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, and ticlopidine hydrochloride. Other drugs suitable for use and meeting the solubility parameters described above will be apparent to those skilled in the art. Drugs of particular interest are metformin hydrochloride and sertraline hydrochloride. The drug loadings (weight percent of drug relative to total of drug and polymer) in most of these cases will be about 80% or less.

The invention is also of use with drugs that have been formulated to include additives that impart a small degree of hydrophobic character, to further retard the release rate of the drug into the gastric fluid. One example of such a release rate retardant is glyceryl monostearate. Other examples are fatty acids and salts of fatty acids, one example of which is sodium myristate. The quantities of these additives when present can vary; and in most cases, the weight ratio of additive to drug will range from about 1:10 to about 2:1, and preferably from about 1:8 to about 1:2.

The water-swellable polymer forming the matrix in accordance with this invention is any polymer that is non-toxic, that swells in a dimensionally unrestricted manner upon imbibition of water, and that provides for sustained release of an incorporated drug. Polymers having molecular weights of about 4,500,000 and higher are preferred. More preferred are polymers with molecular weights within the range of about 4,500,000 to about 10,000,000, and even more preferred are polymers with molecular weights within

the range of about 5,000,000 to about 8,000,000. In many cases, polymers are more commonly characterized in terms of the viscosity of polymer solutions at a given concentration and temperature. Preferred viscosity ranges for various classes of polymers are given below. Examples of polymers suitable for use in this invention are cellulose polymers and their derivatives, polysaccharides and their derivatives, polyalkylene oxides, and crosslinked polyacrylic acids and their derivatives.

The term "cellulose" is used herein to denote a linear polymer of anhydroglucose. Preferred cellulose polymers are alkyl-substituted cellulose polymers that ultimately dissolve in the gastrointestinal (G.I.) tract in a predictably delayed manner. Preferred alkyl-substituted cellulose derivatives are those substituted with alkyl groups of 1 to 3 carbon atoms each. Examples are methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose. In terms of their viscosities, one class of preferred alkyl-substituted celluloses includes those whose viscosity is within the range of about 100 to about 110,000 centipoise as a 2% aqueous solution at 20°C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20°C. Particularly preferred alkyl-substituted celluloses are hydroxyethylcellulose and hydroxypropylmethylcellulose. A presently preferred hydroxyethylcellulose is NATRASOL® 250HX NF (National Formulary), available from Aqualon Company, Wilmington, Delaware, USA.

Polyalkylene oxides of greatest utility in this invention are those having the properties described above for alkyl-substituted cellulose polymers. A particularly preferred polyalkylene oxide is poly(ethylene oxide), which term is used herein to denote a linear polymer of unsubstituted ethylene oxide. Preferred poly(ethylene oxide)s are those with a weight-average molecular weight within the range of about 9×10^5 to about 8×10^6. Poly(ethylene oxide)s are often characterized by their viscosity in solution. For purposes of this invention, a preferred viscosity range is about 50 to about 2,000,000 centipoise for a 2% aqueous solution at 20°C. Two presently preferred poly(ethylene oxide)s are POLYOX® NF, grade WSR Coagulant, molecular weight 5 million, and grade WSR 303, molecular weight 7 million, both products of Union Carbide Chemicals and Plastics Company Inc. of Danbury, Connecticut, USA.

Polysaccharide gums, both natural and modified (semi-synthetic) can be used. Examples are dextran, xanthan gum, gellan gum, welan gum and rhamsan gum. Xanthan gum is preferred.

Crosslinked polyacrylic acids of greatest utility are those whose properties are the same as those described above for alkyl-substituted cellulose and polyalkylene oxide polymers. Preferred crosslinked polyacrylic acids are those with a viscosity ranging from about 4,000 to about 40,000 centipoise for a 1% aqueous solution at 25°C. Three

presently preferred examples are CARBOPOL® NF grades 971P, 974P and 934P (BFGoodrich Co., Specialty Polymers and Chemicals Div., Cleveland, Ohio, USA). Further examples are polymers known as WATER LOCK®, which are starch/acrylates/-acrylamide copolymers available from Grain Processing Corporation, Muscatine, Iowa, USA.

The hydrophilicity and water swellability of these polymers cause the drug-containing matrices to swell in size in the gastric cavity due to ingress of water in order to achieve a size that will be retained in the stomach when introduced during the fed mode. These qualities also cause the matrices to become slippery, which provides resistance to peristalsis and further promotes their retention in the stomach. The release rate of a drug from the matrix is primarily dependent upon the rate of water imbibition and the rate at which the drug dissolves and diffuses from the swollen polymer, which in turn is related to the solubility and dissolution rate of the drug, the drug particle size and the drug concentration in the matrix. Also, because these polymers dissolve very slowly in gastric fluid, the matrix maintains its integrity over at least a substantial period of time, in many cases at least 90% and preferably over 100% of the dosing period. The particles will then slowly dissolve or decompose. In most cases, complete dissolution or decomposition will occur within 8 to 10 hours after the intended dosing period.

The amount of polymer relative to the drug can vary, depending on the drug release rate desired and on the polymer, its molecular weight, and excipients that may be present in the formulation. The amount of polymer will be sufficient however to retain at least about 40% of the drug within the matrix one hour after ingestion (or immersion in the gastric fluid). Preferably, the amount of polymer is such that at least 50% of the drug remains in the matrix one hour after ingestion. More preferably, at least 60%, and most preferably at least 80%, of the drug remains in the matrix one hour after ingestion. In all cases, however, the drug will be substantially all released from the matrix within about eight hours after ingestion, and the polymeric matrix will remain substantially intact until all of the drug is released. The term "substantially intact" is used herein to denote a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles.

The water-swellable polymers can be used individually or in combination. Certain combinations will often provide a more controlled release of the drug than their components when used individually. Examples are cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum. Another example is poly(ethylene oxide) combined with xanthan gum.

The benefits of this invention will be achieved at drug loadings of about 80% or less (*i.e.*, the weight percent of drug relative to total of drug and polymer), with preferred

loadings within the range of 15% to 80%, more preferably within the range of 30% to 80%, and most preferably in certain cases within the range of about 30% to 70%.

The formulations of this invention may assume the form of particles, tablets, or particles retained in capsules. A preferred formulation consists of particles consolidated into a packed mass for ingestion, even though the packed mass will separate into individual particles after ingestion. Conventional methods can be used for consolidating the particles in this manner. For example, the particles can be placed in gelatin capsules known in the art as "hard-filled" capsules and "soft-elastic" capsules. The compositions of these capsules and procedures for filling them are known among those skilled in drug formulations and manufacture. The encapsulating material should be highly soluble so that the particles are freed and rapidly dispersed in the stomach after the capsule is ingested.

One presently preferred dosage form is a size 0 gelatin capsule containing either two or three pellets of drug-impregnated polymer. For two-pellet capsules, the pellets are cylindrically shaped, 6.6 or 6.7 mm (or more generally, 6.5 to 7 mm) in diameter and 9.5 or 10.25 mm (or more generally, 9 to 12 mm) in length. For three-pellet capsules, the pellets are again cylindrically shaped, 6.6 mm in diameter and 7 mm in length. For a size 00 gelatin capsule with two pellets, the pellets are cylindrical, 7.5 mm in diameter and 11.25 mm in length. For a size 00 gelatin capsule with three pellets, the pellets are cylindrical, 7.5 mm in diameter and 7.5 mm in length. Another presently preferred dosage form is a single, elongated tablet, with dimensions 18 to 22 mm in length, 6.5 to 7.8 mm in width, and 6.2 to 7.5 mm in height. A preferred set of dimensions is 20 mm in length, 6.7 mm in width, and 6.4 mm in height. These are merely examples; the shapes and sizes can be varied considerably.

The particulate drug/polymer mixture or drug-impregnated polymer matrix can be prepared by various conventional mixing, comminution and fabrication techniques readily apparent to those skilled in the chemistry of drug formulations. Examples of such techniques are as follows:

(1) Direct compression, using appropriate punches and dies, such as those available from Elizabeth Carbide Die Company, Inc., McKeesport, Pennsylvania, USA; the punches and dies are fitted to a suitable rotary tableting press, such as the Elizabeth-Hata single-sided Hata Auto Press machine, with either 15, 18 or 22 stations, and available from Elizabeth-Hata International, Inc., North Huntington, Pennsylvania, USA; and

(2) Injection or compression molding using suitable molds fitted to a compression unit, such as those available from Cincinnati Milacron, Plastics Machinery Division, Batavia, Ohio, USA.

When particles are made by direct compression, the addition of lubricants may be helpful and sometimes important to promote powder flow and to prevent capping of the

particle (breaking off of a portion of the particle) when the pressure is relieved. Useful lubricants are magnesium stearate (in a concentration of from 0.25% to 3% by weight, preferably less than 1% by weight, in the powder mix), and hydrogenated vegetable oil (preferably hydrogenated and refined triglycerides of stearic and palmitic acids at about 1% to 5% by weight, most preferably about 2% by weight. Additional excipients may be added to enhance powder flowability and reduce adherence.

The term "dosage form" denotes any form of the formulation that contains an amount sufficient to achieve a therapeutic effect with a single administration. When the formulation is a tablet or capsule, the dosage form is usually one such tablet or capsule. The frequency of administration that will provide the most effective results in an efficient manner without overdosing will vary with the characteristics of the particular drug, including both its pharmacological characteristics and its physical characteristics such as solubility, and with the characteristics of the swellable matrix such as its permeability, and the relative amounts of the drug and polymer. In most cases, the dosage form will be such that effective results will be achieved with administration no more frequently than once every eight hours or more, preferably once every twelve hours or more, and even more preferably once every twenty-four hours or more.

As indicated above, the dosage forms of the present invention find their greatest utility when administered to a subject who is in the digestive or "fed" mode. During this mode, particulate matter above a certain minimum particle size is retained in the subject's stomach. The fed mode is distinguished from the fasting mode, which prevails during nighttime rest and into the early morning hours. The fasting mode is characterized by interdigestive migrating motor complex (MMC) waves, which are intense contractions beginning midway down the stomach and continuing down the intestinal tract to the distal ileum, clearing the stomach of digested materials as well as indigestible solids within a certain size range that would be retained if the stomach were in the fed mode. The fed mode is initiated by the ingestion of food, and causes suspension of the MMC waves, thereby permitting the stomach to retain the particulate matter long enough to be broken down and at least partially digested. When the fed mode passes, the MMC waves of the fasting mode resume.

The fed mode can be initiated by a signal triggered by the ingestion of food, or by a chemical signal based on nutrient and osmotic factors, which can be supplied with the ingestion of food or administered specifically to initiate the fed mode. These factors include hypertonic solutions, acid, fat, certain carbohydrates, and certain amino acids. Fat is the most powerful of these factors, relaxing the fundus with lower intragastric pressure, increasing the reservoir function of the proximal stomach, contracting the pyloric sphincter, and changing intestinal peristalsis from a propagated series of waves to segmenting activity.

The following examples are offered for purposes of illustration, and are not intended to limit the invention in any manner.

EXAMPLE 1

This example illustrates the controlled-release behavior of metformin hydrochloride, a highly soluble drug (whose solubility is approximately 35%), from a polymeric matrix consisting of poly(ethylene oxide). Three different dose levels were prepared -- systems designed to release 90% of their drug contents at approximately 3 hours, 6 hours, and 8 hours, respectively.

Drug and polymer, with 0.5% magnesium stearate as a tableting lubricant, were compressed into pellets measuring 7.2 mm diameter × 8.8 mm length and weighing 390 mg for samples designed for 3-hour and 6-hour release, and 7.4 mm diameter × 8.5 mm length and weighing 380 mg for samples designed for 8-hour release, and two pellets of a given type were incorporated into a single gelatin capsule. Thus, three different types of gelatin capsule were prepared as follows:

$t_{90\%} \cong$ 3 hours:

metformin hydrochloride		250.00 mg
POLYOX® 1105,		
molecular weight 900,000		138.67
magnesium stearate		1.95
	Total:	390.62 mg

$t_{90\%} \cong$ 6 hours:

metformin hydrochloride		250.00 mg
POLYOX® Coagulant,		
molecular weight 5,000,000		138.67
magnesium stearate		1.95
	Total:	390.62 mg

$t_{90\%} \cong$ 8 hours:

metformin hydrochloride		125.00 mg
POLYOX® 303,		
molecular weight 7,000,000		266.11
magnesium stearate		1.97
	Total:	393.08 mg

Release rate tests on each of these three formulations were performed in modified artificial gastric fluid by the following procedure.

Dissolution was performed in a USP Apparatus 2, modified to include a stainless steel cone (7/8 inch in height and 7/8 inch in diameter at the base) at the bottom of each vessel, placed directly beneath the paddle shaft to eliminate the "dead zone" effect. A paddle speed of 60 rpm and a bath temperature of 37.4°C were used. The gelatin capsule was opened and the individual pellets and empty gelatin capsule were dropped into the dissolution vessel containing 900 mL of modified simulated gastric fluid (7 mL of hydrochloric acid and 2 g of sodium chloride in 100 mL of deionized water; the enzyme pepsin was omitted). Once the pellets had settled to the bottom of the vessel, the paddle rotation was initiated. Samples 5 mL in size were taken at specified time points, and the sample volumes were not replaced. The samples were diluted as necessary for quantitative analysis by HPLC.

The results are shown in FIG. 1, where the filled diamonds represent the $t_{90\%} \cong 3$ formulation, the ×'s represent the $t_{90\%} \cong 6$ formulation, and the open circles represent the $t_{90\%} \cong 8$ formulation. The curves show that the $t_{90\%}$ value of the first formulation was fairly close to 3.5 hours, the $t_{90\%}$ value of the second formulation was fairly close to 6.0 hours, and $t_{90\%}$ value of the third formulation was fairly close to 7.5 hours.

EXAMPLE 2

This example illustrates the controlled-release behavior of captopril from a polymeric matrix consisting of poly(ethylene oxide), both with and without glyceryl monostearate (8% by weight). The formulations used were as follows:

1.	Captopril	925.0 mg
	Poly(ethylene oxide) (POLYOX® 301), molecular weight 4,000,000	4,075.0
	Total	5,000.00 mg
2.	Captopril	925.0 mg
	glyceryl monostearate	150.0
	Poly(ethylene oxide) (POLYOX® 301), molecular weight 4,000,000	3,925.0
	Total	5,000.0 mg

Each formulation was compressed into a tablet measuring 6.0 mm diameter × 6.7 mm length and weighing 180 mg. Release rate tests on each of the two tablets were performed in modified simulated gastric fluid by the procedure of Example 1, except that the paddle rotation speed was 30 rpm and the tablets were dropped directly into the dissolution vessel.

The results are shown in FIG. 2, where the filled squares represent Formulation No. 1 consisting of captopril and poly(ethylene oxide) only, and the open circles represent Formulation No. 2 which further contained glyceryl monostearate.

EXAMPLE 3

This example illustrates the controlled-release behavior of captopril from a polymeric matrix of hydroxyethyl cellulose with the inclusion of glyceryl monostearate, but at varying pellet sizes. The formulation contained 19% captopril (all percents by weight) and 4.8% glyceryl monostearate in hydroxyethyl cellulose of molecular weight within the range of 1,000,000 to 1,500,000. The pellet sizes and weights were (a) 3.3 mm diameter × 3.5 mm length at 35 mg (referred to herein as 3-mm tablets), (b) 4.3 mm diameter × 4.9 mm length at 75 mg (referred to herein as 4-mm tablets), and (c) 6.3 mm diameter × 6.5 mm length at 187 mg (referred to herein as 6-mm tablets).

Release rate tests on each of the three tablet sizes (fifteen of the 3-mm tablets, seven of the 4-mm tablets, and three of the 6-mm tablets) were performed using the procedures of Example 1, except that a weighted watchglass was used in place of the stainless steel cone, and analyses of the samples were performed by UV/Vis. The results are shown in FIG. 3, where the filled squares represent the 3-mm pellets, the filled triangles the 4-mm pellets, and the filled circles the 6-mm pellets. This demonstrates the variation of pellet size as a further means of varying the release pattern, the larger pellets having less surface area.

EXAMPLE 4

This example further illustrates the controlled release of metformin hydrochloride, using a higher drug loading, and various polymers and combinations of polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. 4 where the results are plotted, were as follows (all percentages are by weight):

Filled circles: 79.6% metformin HCl; 20% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.4% magnesium stearate. Pellet dimensions 6.04 mm diameter × 9.48 mm length; containing approximately 478 mg metformin HCl.

Filled squares: 79.6% metformin HCl; 20% xanthan gum (KELTROL® F, Kelco, Div. of Merck & Co., Inc., San Diego, California, USA); 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter × 9.40 mm length; containing approximately 483 mg metformin HCl.

Plus signs: 79.6% metformin HCl; 20% hydroxypropylmethyl cellulose (BENECEL® 824, Aqualon Co., Wilmington, Delaware, USA), viscosity (2%, 20°C) 11,000 to 15,000 cps; 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter × 9.49 mm length; containing approximately 480 mg metformin HCl.

Open diamonds: 79.6% metformin HCl; 5% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 15% poly(ethylene oxide (POLYOX® 303, molecular weight 7,000,000); 0.4% magnesium stearate. Pellet dimensions 6.06 mm diameter × 9.60 mm length; containing approximately 480 mg metformin HCl.

×'s: 79.6% metformin HCl, 18.05% xanthan gum (KELTROL® F); 1.99% WATER LOCK® D-223 (starch graft poly(2-propenamide-co-2-propenoic acid)), mixed sodium and aluminum salts, Grain Processing Corporation, Muscatine, Iowa, USA); 0.4% magnesium stearate. Pellet dimensions were 6.06 mm diameter × 9.24 mm length; containing approximately 476 mg metformin HCl total.

EXAMPLE 5

This example further illustrates the controlled release of metformin hydrochloride from a single capsule-shaped tablet. The procedures used were the same as those described above, and the resulting curve is plotted in FIG. 5. The formulation was as follows (all percentages are by weight): 64% metformin HCl; 35.5% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate; plus an additional 2% OPADRY® Clear coating (hydroxypropyl methylcellulose, Colorcon, West Point, Pennsylvania, USA). The tablet dimensions were 6.48 mm diameter × 7.20 mm height × 19.21 mm length, and contained approximately 506 mg metformin HCl per tablet.

EXAMPLE 6

This example further illustrates the controlled release of captopril, using various polymers and combinations of polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. 6 where the results are plotted, were as follows (all percentages are by weight):

Plus signs: 80% captopril; 20% hydroxypropylmethyl cellulose (BENECEL® 824, viscosity (2%, 20°C) 11,000 to 15,000 cps). Pellet dimensions: 6.03 mm diameter × 9.25 mm length, 2 pellets weighing 293 mg each, containing approximately 468.6 mg captopril total.

Filled diamonds: 80% captopril; 20% xanthan gum (KELTROL® F). Pellet dimensions: 6.04 mm diameter × 9.18 mm length, 2 pellets weighing 299 mg each, containing approximately 477.8 mg captopril total.

Filled triangles: 80% captopril; 20% hydroxyethyl cellulose (250HX, molecular weight 1,000,000). Pellet dimensions: 6.03 mm diameter × 9.53 mm length, 2 pellets weighing 299 mg each, containing approximately 478.2 mg captopril total.

Open circles: 80% captopril; 20% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000). Pellet dimensions: 6.04 mm diameter × 9.59 mm length, 2 pellets weighing 301 mg each, containing approximately 481.6 mg captopril total.

Filled squares: 80% captopril; 20% carboxymethyl cellulose (12M31P, molecular weight 250,000). Pellet dimensions: 6.04 mm diameter × 9.18 mm length, 2 pellets weighing 299 mg each, containing approximately 477.6 mg captopril total.

Open triangles: 79.93% captopril; 10.03% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10.04% xanthan gum (KELTROL® F). Pellet dimensions: 6.04 mm diameter × 9.26 mm length, 2 pellets weighing 296 mg each, containing approximately 478.2 mg captopril total.

×'s: 79.96% captopril; 10.03% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10.01% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000). Pellet dimensions: 6.04 mm diameter × 9.41 mm length, 2 pellets weighing 297 mg each, containing approximately 483 mg captopril total.

Dashes: 80% captopril; 10% hydroxyethyl cellulose (250HX, molecular weight 1,000,000); 10% hydroxypropylmethyl cellulose (BENECEL® 824, viscosity (2%, 20°C) 11,000 to 15,000 cps). Pellet dimensions: 6.04 mm diameter × 9.41 mm length, 2 pellets weighing 298 mg each, containing approximately 476.6 mg captopril total.

Open diamonds: 79.96% captopril; 18.05% xanthan gum (KELTROL® F); 1.99% WATERLOCK® D-223. Pellet dimensions: 6.04 mm diameter × 9.16 mm length, 2 pellets weighing 297 mg each, containing approximately 475 mg captopril total.

EXAMPLE 7

This example presents further data on metformin hydrochloride formulations, illustrating the effect of lower drug loadings than those used in the preceding examples. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. 7 where the results are plotted, were as follows (all percentages are by weight):

Filled squares: 32.5% metformin HCl; 67% poly(ethylene oxide) (POLYOX® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions 6.62 mm diameter × 10.40 mm length, 2 pellets weighing 400 mg each, containing approximately 260 mg metformin HCl total.

Open circles: 32.5% metformin HCl; 67% xanthan gum (KELTROL® F); 0.5% magnesium stearate. Pellet dimensions 6.65 mm diameter × 9.28 mm length; 2 pellets weighing 401 mg each, containing approximately 261 mg metformin HCl total.

EXAMPLE 8

This example illustrates the sustained release of vancomycin hydrochloride from various polymers. The procedures used were the same as those described above, and the formulations together with the symbols used in FIG. 8 where the results are plotted, were as follows (all percentages are by weight):

Open squares: 31.5% vancomycin hydrochloride; 68% poly(ethylene oxide) (POLYOX ® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter × 10.23 mm length, 2 pellets weighing 403 mg each, containing approximately 253 mg vancomycin hydrochloride total.

Open triangles: 31.5% vancomycin hydrochloride; 68% poly(ethylene oxide) (POLYOX ® 301, molecular weight 4,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter × 10.28 mm length, 2 pellets weighing 402 mg each, containing approximately 253 mg vancomycin hydrochloride total.

×'s: 31.5% vancomycin hydrochloride; 68% hydroxypropyl methylcellulose (BENECEL® 824, viscosity 11,000-15,000 cps (2% solution at 20°C)); 0.5% magnesium stearate. Pellet dimensions: 6.59 mm diameter × 10.10 mm length, 2 pellets weighing 405 mg each, containing approximately 255 mg vancomycin hydrochloride total.

Open circles: 31.5% vancomycin hydrochloride; 68% xanthan gum (KELTROL® F); 0.5% magnesium stearate. Pellet dimensions: 6.62 mm diameter × 9.77 mm length, 2 pellets weighing 401 mg each, containing approximately 253 mg vancomycin hydrochloride total.

Filled squares: 62.5% vancomycin hydrochloride; 37% poly(ethylene oxide) (POLYOX ® 303, molecular weight 7,000,000); 0.5% magnesium stearate. Pellet dimensions: 6.60 mm diameter × 10.01 mm length, 2 pellets weighing 409 mg each, containing approximately 508 mg vancomycin hydrochloride total.

In the prior art, vancomycin and its salts are administered by injection, due to poor absorption when administered orally. By providing for all or at least a portion of the total administered amount to be delivered by controlled delivery in the gastric retentive system of this invention, that portion so delivered is directed to the proximal portion of the small intestine, the most efficient site for absorption of this drug, resulting in an enhanced absorption from the oral dosage form of the invention.

The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art that the components, additives, proportions, methods of formulation, and other parameters of the invention can be modified further or substituted in various ways without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A controlled-release oral drug dosage form for releasing a drug whose solubility in water is such that one part of said drug dissolves in less than ten parts by weight of water, said dosage form comprising a solid polymeric matrix in which said drug is dispersed at a weight ratio of drug to polymer of about 80:20 or less, said polymeric matrix being one that swells to at least about twice its volume upon imbibition of water, that releases said drug into gastric fluid by the dissolution and diffusion of said drug out of said matrix by said gastric fluid, that upon immersion in gastric fluid retains at least about 40% of said drug one hour after such immersion and releases substantially all of said drug within about eight hours after such immersion, and that remains substantially intact until all of said drug is released.

2. A dosage form of claim 1 in which the solubility of said drug in water is such that one part of said drug dissolves in less than about five parts by weight of water.

3. A dosage form of claim 1 in which the solubility of said drug in water is such that one part of said drug dissolves in less than about three parts by weight of water.

4. A dosage form of claim 1 in which said drug is a member selected from the group consisting of metformin hydrochloride, vancomycin hydrochloride, captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, and ticlopidine hydrochloride.

5. A dosage form of claim 1 in which said drug is metformin hydrochloride.

6. A dosage form of claim 1 in which said drug is sertraline hydrochloride.

7. A dosage form of claim 1 in which said drug is captopril.

8. A dosage form of claim 1 in which said drug is vancomycin hydrochloride.

9. A dosage form of claim 1 in which said polymeric matrix is formed of a polymer selected from the group consisting of poly(ethylene oxide), xanthan gum, cellulose, alkyl-substituted celluloses, and crosslinked polyacrylic acids.

10. A dosage form of claim **1** in which said polymeric matrix is formed of a polymer selected from the group consisting of poly(ethylene oxide), xanthan gum, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose.

11. A dosage form of claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight of at least about 4,500,000.

12. A dosage form of claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight in the range of about 4,500,000 to about 10,000,000.

13. A dosage form of claim **1** in which said polymeric matrix is formed of poly(ethylene oxide) at a molecular weight in the range of about 5,000,000 to about 8,000,000.

14. A dosage form of claim **1** in which said weight ratio of drug to polymer is from about 15:85 to about 80:20.

15. A dosage form of claim **1** in which said weight ratio of drug to polymer is from about 30:70 to about 80:20.

16. A dosage form of claim **1** in which said weight ratio of drug to polymer is from about 30:70 to about 70:30.

17. A dosage form of claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 50% of said drug one hour after such immersion.

18. A dosage form of claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 60% of said drug one hour after such immersion.

19. A dosage form of claim **1** in which said polymeric matrix upon immersion in gastric fluid retains at least about 80% of said drug one hour after such immersion.

20. A dosage form of claim **1** further comprising a hydrophobic additive formulated with said drug to further retard the release of said drug to said gastric fluid.

21. A dosage form of claim **1** in which said polymeric matrix consists of two cylindrical tablets, each measuring about 9 mm to about 12 mm in length and about 6.5 mm to about 7 mm in diameter.

22. A dosage form of claim **1** in which said polymeric matrix consists of a single elongated tablet measuring about 18 mm to about 22 mm in length, about 6.5 mm to about 7.8 mm in width, and about 6.2 to 7.5 mm in height.

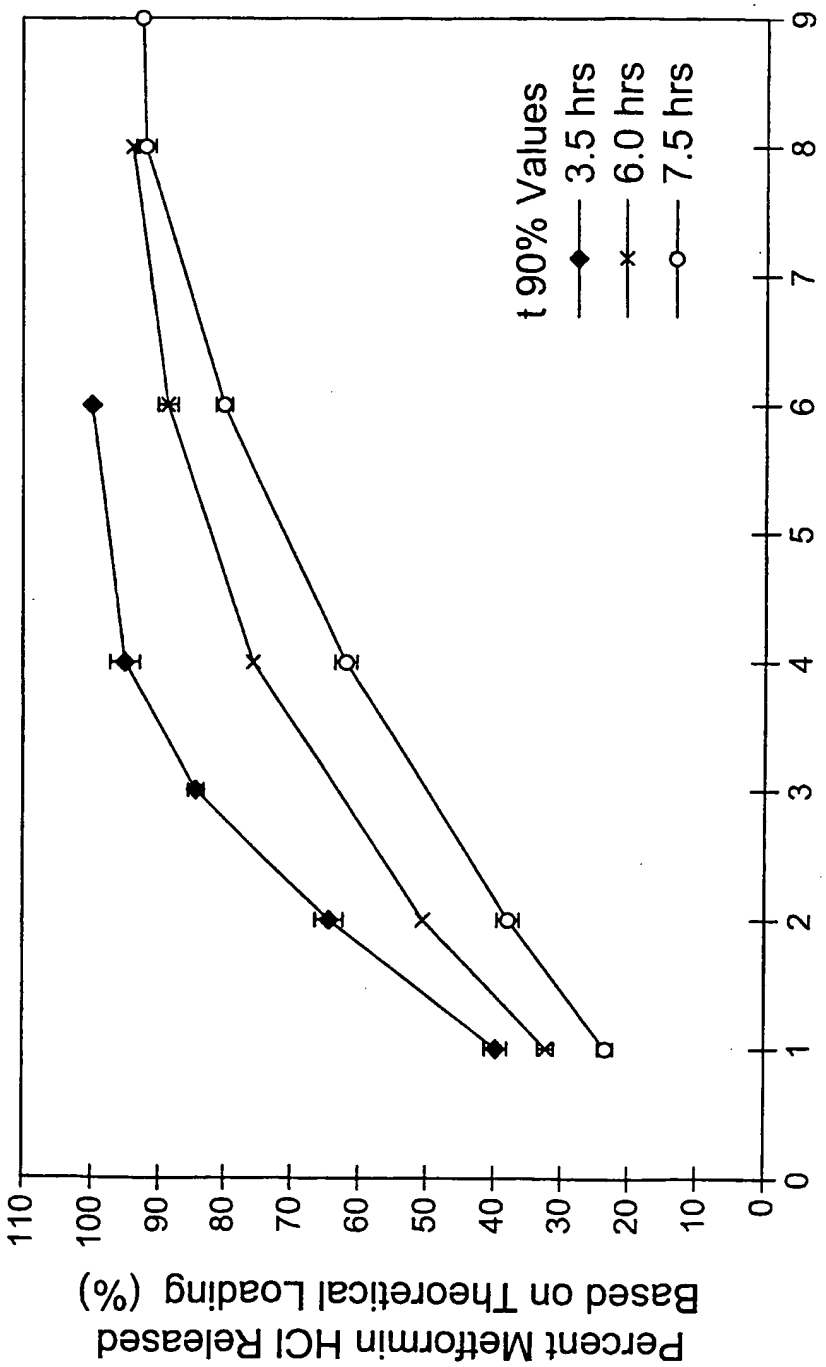
Percent Metformin HCl Released
Based on Theoretical Loading (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
Time (hr)
t 90% Values
3.5 hrs
6.0 hrs
7.5 hrs

Fig. 1

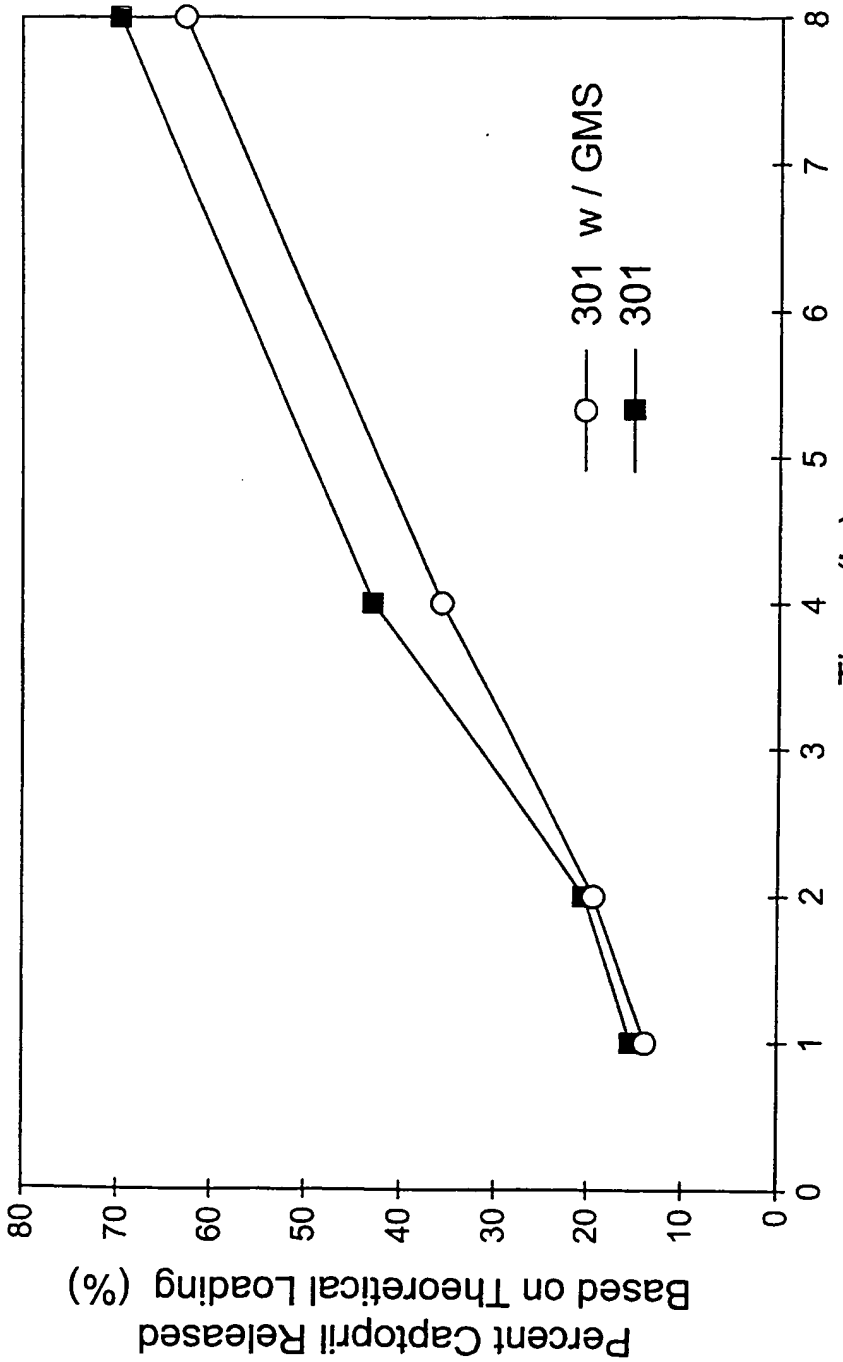
Percent Captopril Released
Based on Theoretical Loading (%)
0
10
20
30
40
50
60
70
80
0
1
2
3
4
5
6
7
8
Time (hr)
301 w / GMS
301

Fig. 2

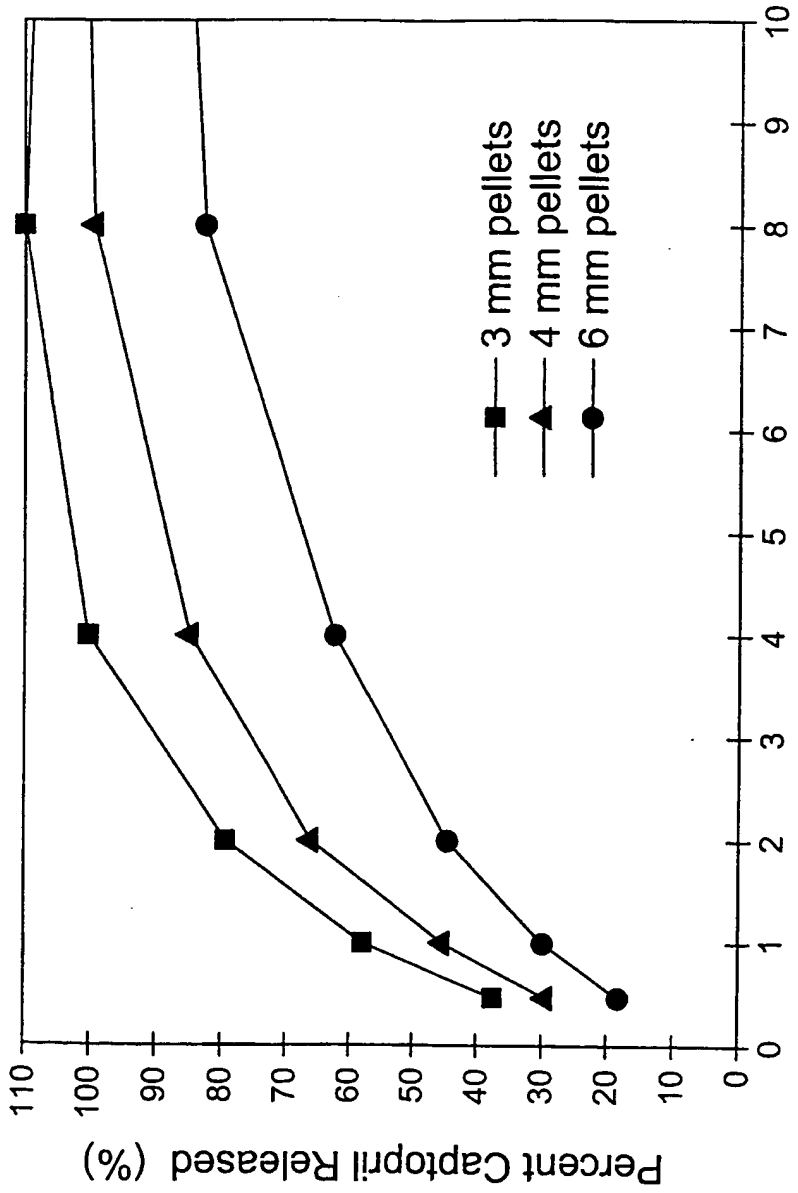
Percent Captopril Released (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)
3 mm pellets
4 mm pellets
6 mm pellets

Fig. 3

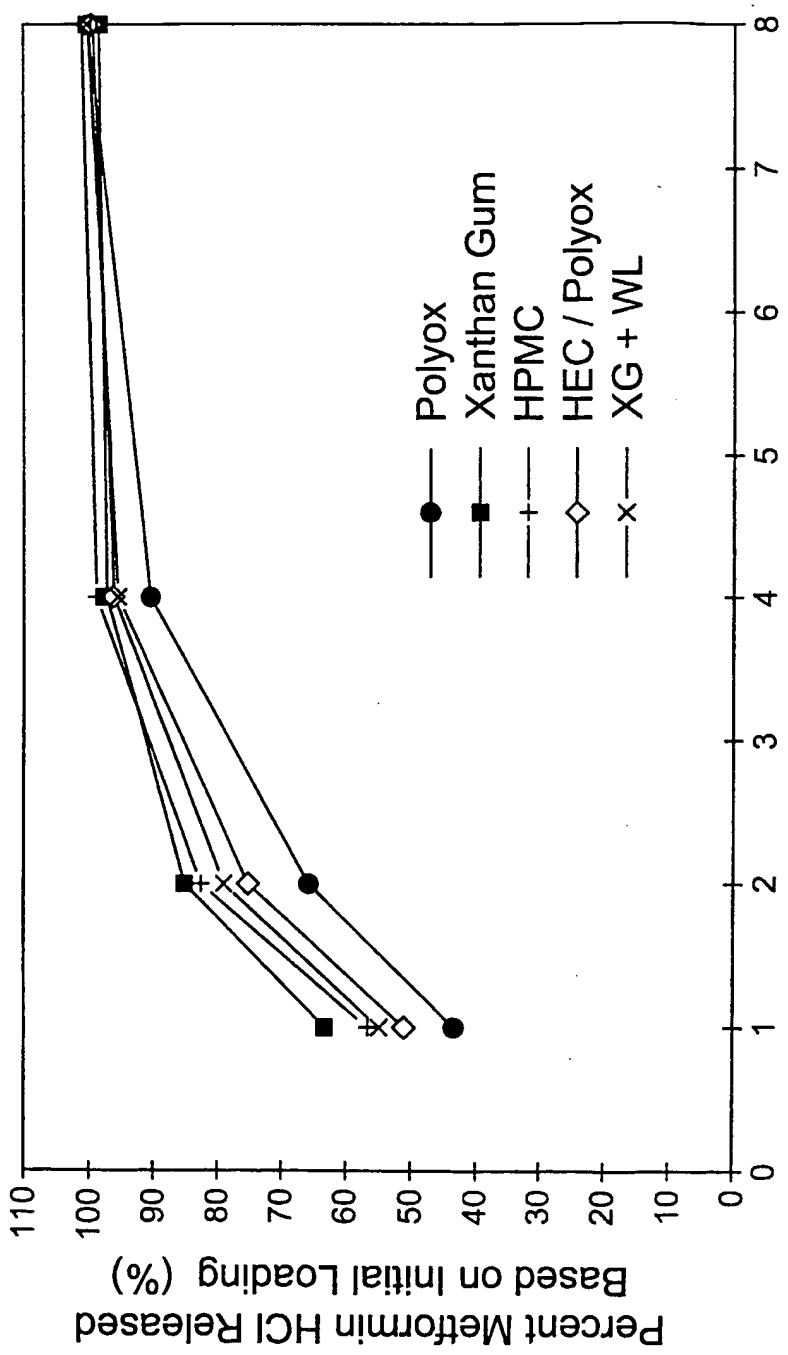
Percent Metformin HCl Released
Based on Initial Loading (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
Time (hr)
Polyox
Xanthan Gum
HPMC
HEC / Polyox
XG + WL

Fig. 4

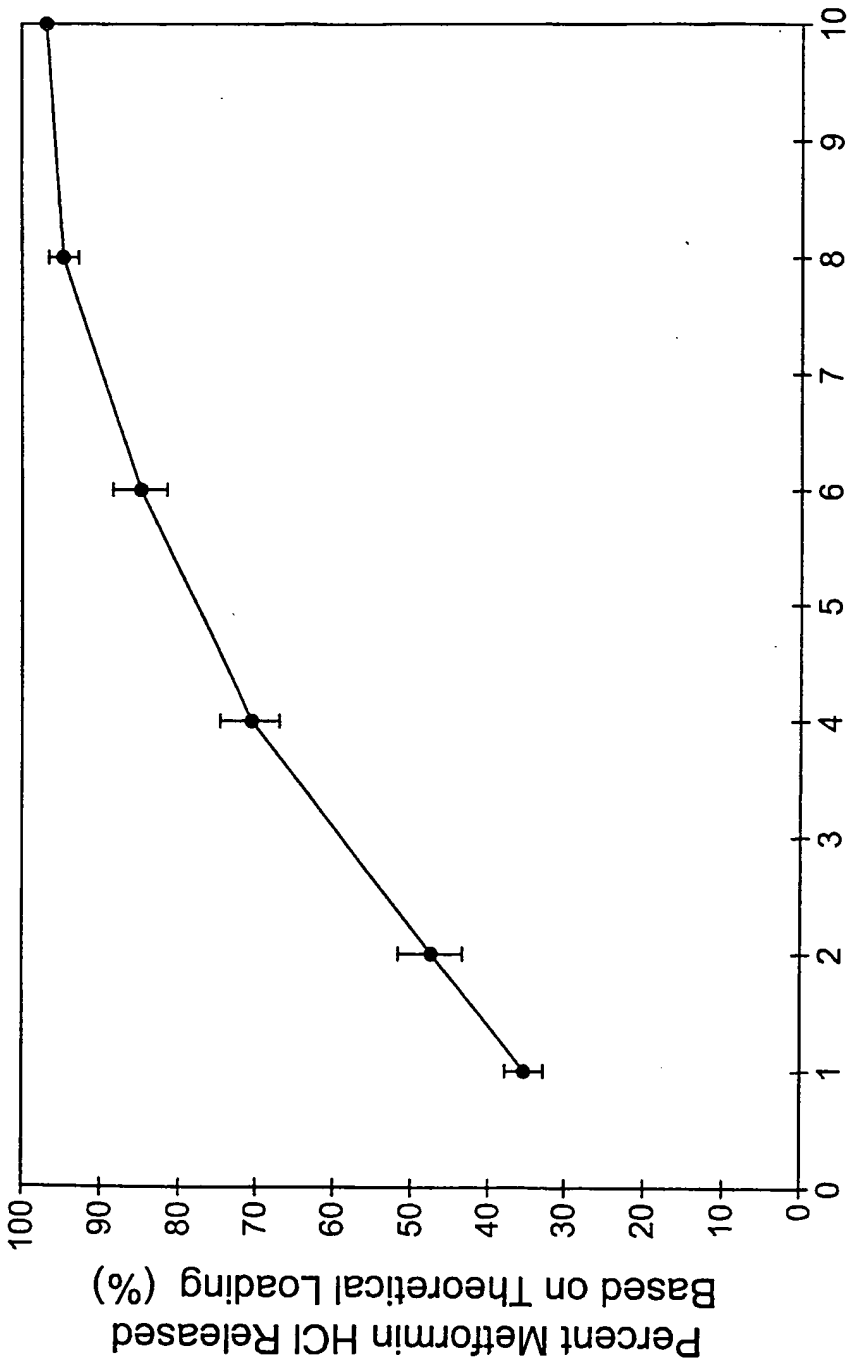
Percent Metformin HCl Released
Based on Theoretical Loading (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)

Fig. 5

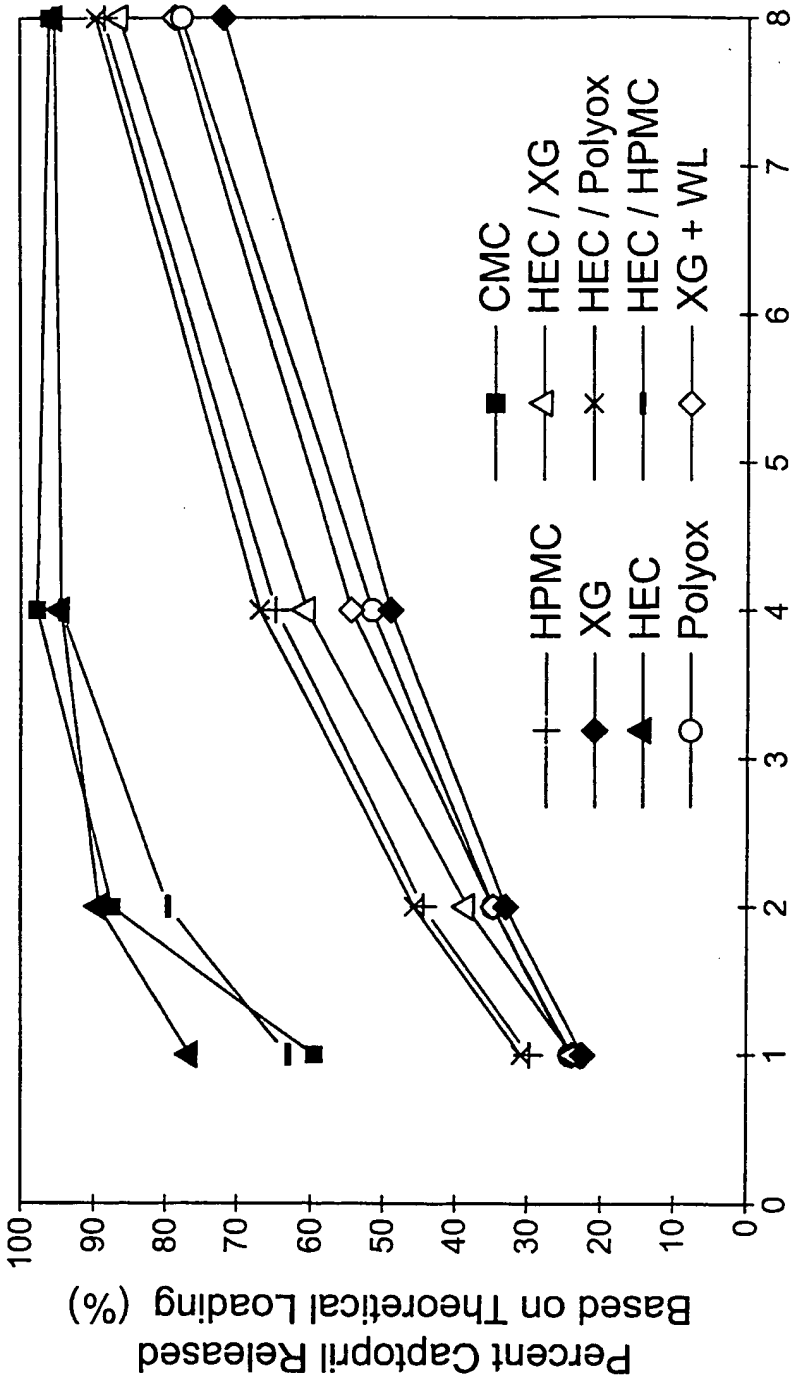
Percent Captopril Released
Based on Theoretical Loading (%)
Time (hr)
CMC
HEC / XG
HEC / Polyox
HEC / HPMC
XG + WL
HPMC
XG
HEC
Polyox

Fig. 6

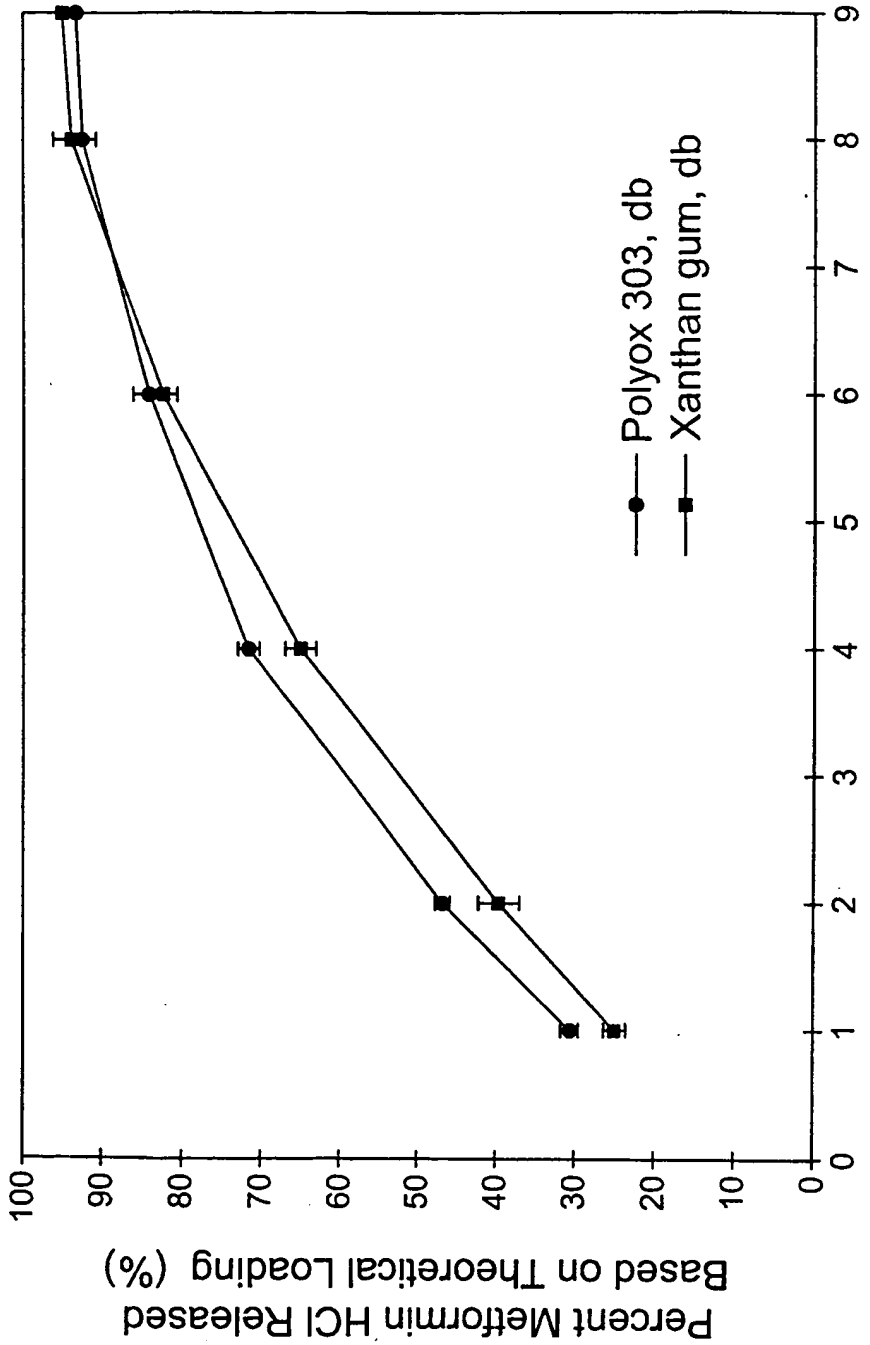
Percent Metformin HCl Released
Based on Theoretical Loading (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
Time (hr)
Polyox 303, db
Xanthan gum, db

Fig. 7

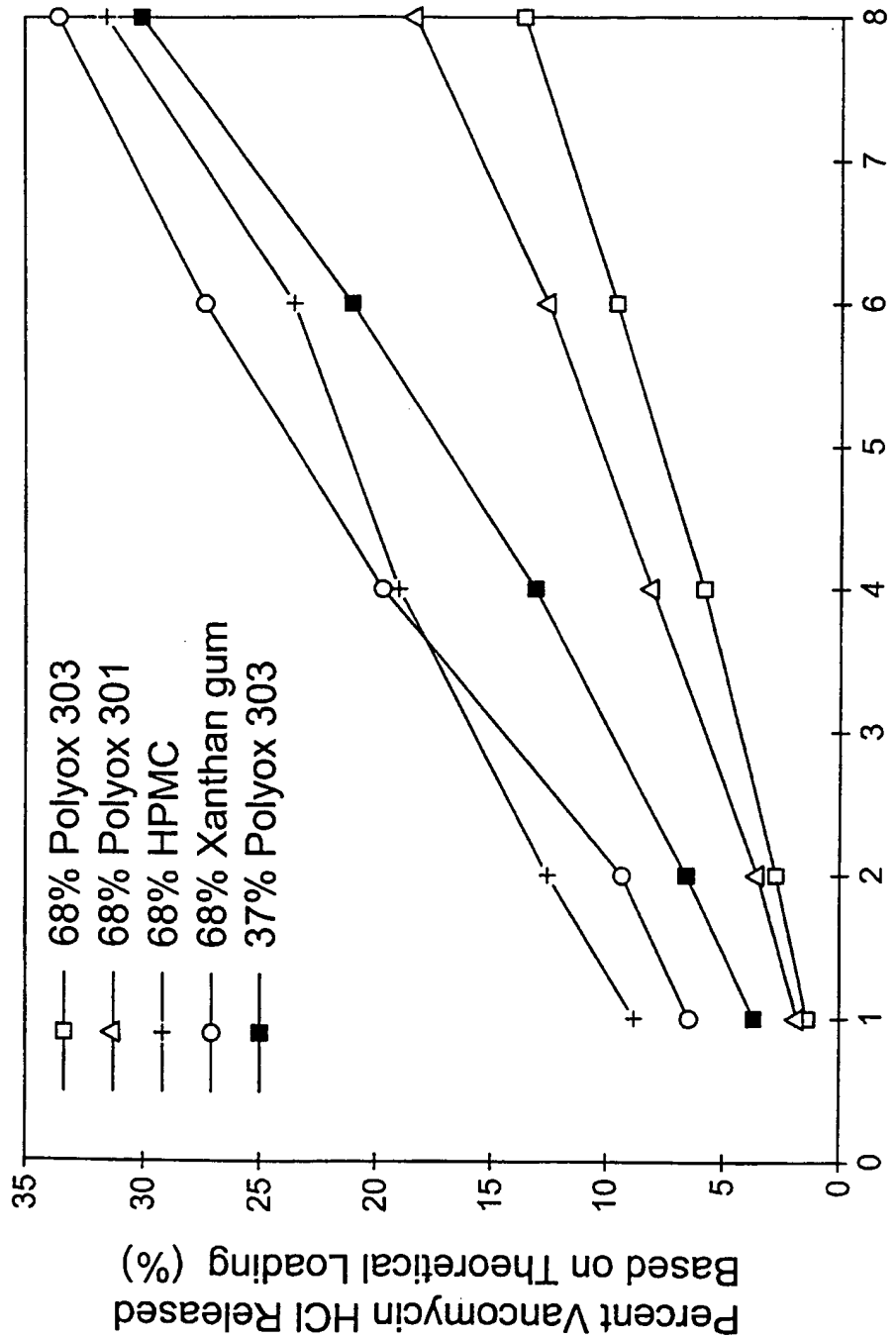
Percent Vancomycin HCl Released
Based on Theoretical Loading (%)
35
30
25
20
15
10
5
0
0
1
2
3
4
5
6
7
8
Time (hr)
68% Polyox 303
68% Polyox 301
68% HPMC
68% Xanthan gum
37% Polyox 303

Fig. 8

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 98/11302

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 44 32 757 A (BOEHRINGER MANNHEIM) 21 March 1996 see claims 1-6 see examples 1-7 ---	1-5,9, 10,14-22
X	WO 96 32097 A (PHARMAPASS) 17 October 1996 see claims 1-4,8,19 see page 5, line 32 - line 39 see page 9; example 6 --- -/--	1-4,7, 9-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 September 1998	02/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 98/11302

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	A. APICELLA, ET AL.: "Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release" BIOMATERIALS, vol. 14 , no. 2, 1993, pages 83-90, XP000335514 guildford, surrey, GB see the whole document	1-3,9-22
X	EP 0 761 209 A (J. B. CHEMICALS & PHARMACEUTICALS) 12 March 1997 see claim 1 see examples 1-4	1-4,9, 10,14-22
P,X	WO 98 11879 A (DEPOMED) 26 March 1998 see claims 1,3,4,6	1-4,9-22

1

INTERNATIONAL SEARCH REPORT

....ormation on patent family members

Intern al Application No
PCT/US 98/11302

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DE 4432757 A	21-03-1996	AU 3567295 A	29-03-1996
		WO 9608243 A	21-03-1996
		EP 0781129 A	02-07-1997
		JP 10505604 T	02-06-1998
WO 9632097 A	17-10-1996	AU 5652796 A	30-10-1996
		CA 2218054 A	17-10-1996
		EP 0830129 A	25-03-1998
EP 761209 A	12-03-1997	NONE	
WO 9811879 A	26-03-1998	AU 4428097 A	14-04-1998